REMARKS/ARGUMENTS

Claims 1, 5-7, 9, 11-14, 16-19 and 105 are active in this case.

Support for the amendment defining the traumatic brain injury is found in the specification on page 34, line 10 through page 35, line 6.

Support for the definitions of G-CSF is found in the specification on pages 20-25.

The rejection under 112, first paragraph (enablement) for the administration of G-CSF for the treatment of all diseases encompassed by original Claim 1 is obviated, in part, by the amendment to Claim 1 defining the condition as traumatic brain injury. With respect to the treatment of traumatic brain injury, Applicants disagree with the conclusions underlying the rejection. Nonetheless, it should be appreciated that the claims as presented herein do two things. First, it defines the neurological condition as traumatic brain injury, which as discussed below is enabled by the evidence that G-CSF has a neuroprotective effect. Second, the aspect of the rejection relating to the "derivatives" of G-CSF should no longer be applicable as the claims have been amended to more particularly define these derivatives consistent with the extensive disclosure found in the specification on pages 20-25 and the knowledge in the art, some of which is cited and incorporated into the application by reference.

Concerning the factor administered, it is defined as G-CSF, a protein having at least 90% homology to SEQ ID NO:28 and G-CSF activity, a G-CSF peptidomimetic, G-CSF comprising one or more chemical substituents, G-CSF fused to a second protein, a protein fragment of G-CSF having G-CSF activity, or a modified polypeptide of G-CSF having G-CSF activity.

As discussed in the specification, the structure of both the coding DNA and protein are known as well as methods for recombinantly producing mammalian pluripotent granulocyte colony-stimulating factor (WO 87/01132; U.S. Patent 4,810,643).

The fact that these enzymes with known structures were known, the specification and claims satisfy the written description requirement (see *Capon v. Eshhar* (Fed. Cir. 2005): "When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh."; see also *Falkner v. Inglis,* 79 USPQ2d 1001 (Fed. Cir. 2006): "Recitation of Known Structure Is Not Required" to satisfy written description requirement).

In fact, the specification describes many examples of the various G-CSF functional variants, muteins, and mimetics include functional fragments and variants (e.g., structurally and biologically similar to the wild-type protein and having at least one biologically equivalent domain), chemical derivatives of G-CSF (e.g., containing additional chemical moieties, such as polyethyleneglycol and polyethyleneglycol derivatives thereof, and/or glycosylated forms such as Lenogastrim™), and peptidomimetics of G-CSF (e.g., a low molecular weight compound that mimics a peptide in structure and/or function (see, e.g., Abell, *Advances in Amino Acid Mimetics and Peptidomimetics*, London: JAI Press (1997); Gante, *Peptidmimetica – massgeschneiderte Enzyminhibitoren Angew. Chem.* 106: 1780-1802 (1994); and Olson et al., *J. Med. Chem.* 36: 3039-3049 (1993)).

The specification further describes, Additional examples of G-CSF derivatives include a fusion protein of albumin and G-CSF (Albugranin™), or other fusion modifications such as those disclosed in US Pat No. 6261250); PEG-G-CSF conjugates; those described in WO 00/44785 and Viens et al., *J. of Clin. Oncology*, Vl., Nr. 1, 2002: 24-36; norleucine

analogues of G-CSF, those described in US Pat. No. 5,599,690; G-CSF mimetics, such as those described in WO 99/61445, WO 99/61446, and Tian et al., *Science*, Vol. 281, 1998:257-259; G-CSF muteins , where single or multiple amino acids have been modified, deleted or inserted, as described in US Patent No. 5,214,132 and 5,218,092; those G-CSF derivatives described in US Patent No. 6,261,550 and U.S. Pat. No. 4,810,643; and chimeric molecules, which contain the full sequence or a portion of G-CSF in combination with other sequence fragments, e.g. Leridistim--see, for example, Streeter, et al. (2001) *Exp. Hematol.*, 29, 41-50, Monahan, et al. (2001) Exp. Hematol., 29, 416-24. , Hood, et al. (2001) *Biochemistry*, 40, 13598-606, Farese et al. (2001) *Stem Cells*, 19, 514-21, Farese, et al. (2001) *Stem Cells*, 19, 522-33, MacVittie, et al. (2000) *Blood*, 95, 837-45. Additionally, the G-CSF derivatives include those with the cysteines at positions 17, 36, 42, 64, and 74 (of the 174 amino acid species (SEQ ID NO:37) or of those having 175 amino acids , the additional amino acid being an N-terminal methionine(SEQ ID NO:38)) substituted with another amino acid, (such as serine) as described in United States Patent 6,004,548 , G-CSF with an alanine in the first (N-terminal) position; the modification of at least one amino group in a polypeptide having G-CSF activity as described in EP 0 335 423; G-CSF derivatives having an amino acid substituted or deleted in the N-terminal region of the protein as described in EP 0 272 703; derivatives of naturally occurring G-CSF having at least one of the biological properties of naturally occurring G-CSF and a solution stability of at least 35% at 5 mg/ml in which the derivative has at least Cys^{17} of the native sequence replaced by a Ser^{17} residue and Asp^{27} of the native sequence replaced by a Ser^{27} residue as described in EP 0 459 630; a modified DNA sequence encoding G-CSF where the N-terminus is modified for enhanced expression of protein in recombinant host cells, without changing the amino acid sequence of the protein as described in EP 0 459 630; a G-CSF which is modified by inactivating at least one yeast KEX2 protease processing site for increased yield in recombinant production using

yeast as described in EP 0 243 153; lysine altered proteins as described in U.S. Pat. No. 4,904,584; cysteine altered variants of proteins as described in WO/9012874 (US 5,166,322); the addition of amino acids to either terminus of a G-CSF molecule for the purpose of aiding in the folding of the molecule after prokaryotic expression as described in AU-A-10948/92; substituting the sequence Leu-Gly-His-Ser-Leu-Gly-Ile (SEQ ID NO:11) at position 50-56 of G-CSF with 174 amino acids (SEQ ID NO:37), and position 53 to 59 of the G-CSF with 177 amino acids (SEQ ID NO:39), or/and at least one of the four histadine residues at positions 43, 79, 156 and 170 of the mature G-CSF with 174 amino acids (SEQ ID NO:37) or at positions 46, 82, 159, or 173 of the mature G-CSF with 177 amino acids (SEQ ID NO:39) as described in AU-A-76380/91; and a synthetic G-CSF-encoding nucleic acid sequence incorporating restriction sites to facilitate the cassette mutagenesis of selected regions and flanking restriction sites to facilitate the incorporation of the gene into a desired expression system as described in GB 2 213 821.

As to the aspect of this rejection relating to the treatment of traumatic brain injury (TBI), this is supported by the specification on page 34 coupled with the data presented in the application, e.g. "most neuroprotectants found to be effective in models of experimental stroke are also effective in models of experimental TBI" and "in the light of common pathophysiological and protective processes active in cerebral ischemia and TBI, as well as, a common response to neuroprotective strategies indicates that G-CSF therapy will be effective in TBI."

Further, the neuroprotective activity of G-CSF is demonstrated in example 15 and example 17 of the application.

Meanwhile, further experiments have been performed at Sygnis (formerly Axaron), the assignee of the present application, which demonstrate a beneficial outcome in spinal cord injury (SCI) and reduced neuronal apoptosis (via neuroprotection) due to G-CSF treatment.

Since TBI and SCI, both neurotrauma of the central nervous system, are related in many pathophysiological aspects, these findings on SCI are also supportive for the G-CSF treatment of TBI.

In view of the above and the disclosure presented in the specification, it is requested that this rejection be withdrawn.

The rejection of Claims 101 and 102 under either 35 USC 102(b) or 103(a) based on Konishi is obviated by the cancellation of these two claims.

The rejections under 35 USC 102(b) based on Takeshi et al or Buschmann, the rejection under 35 USC 102(e) based on Chajut are respectfully traversed, and the rejection under 35 USC 102(a) based on DE 100 33 219 are respectfully traversed.

The Takeshi rejection

Takeshi et al mentions the possibility of using EPO, G-CSF and M-CSF for the treatment of dementia, Alzheimer's disease and Parkinsons disease. The mode of action discussed by Takeshi is prolonging cell survival and the stimulation of choline acetyl transferase stimulation. Takeshi, however, does not describe the treatment of traumatic brain injury with G-CSF compounds as is now claimed.

Withdrawal of the rejection is requested.

The Buschmann 102(b) and 103(a) rejections

Buschmann mentions the possibility of using GM-CSF, G-CSF, or M-CSF for the treatment of stroke. The mode of action discussed by Buschmann is arteriogenesis. Buschmann, however, does neither describe the treatment of traumatic brain injury with G-CSF compounds as is now claimed, nor the neuroprotective and neuroregenerative effect of G-CSF as disclosed in the present application.

Moreover, as the secondary references combined with Bushmann in the obviousness rejections under 103(a), i.e., Siren, del Zoppo, Emerich, and Tarkowski, do not make up the

primary deficiency of describing or suggesting the method of treating traumatic brain injury of the cited PCT publication, the claims as presented here would also not have been obvious.

The Chajut rejection

As noted in the Action, Chajut was filed on June 7, 2002 with a claim of benefit to a provisional application filed on June 7, 2001. As explained in the attached Rule 131 Declaration, prior to June 7, 2001 certain named inventors had conceived and reduced to practice the invention using G-CSF for the treatment of traumatic brain injury described and claimed in the above-identified U.S. Patent Application. The conception and reduction to practice is supported by the appended German Offenlegungsschrift DE 100 33 219 A1.

Reconsideration of whether Chajut is actually applicable prior art is requested.

Withdrawal of the rejection is requested.

The DE 100 33 219 rejection

This German patent application was published on January 24, 2002 while the present application claims the benefit of a filing date on December 31, 2002. As explained in the attached Rule 132 Declaration, the relevant disclosure of using G-CSF for the treatment of neurological conditions in DE 100 33 219 A1 published January 24, 2002 as it relates the claims of the above-referenced application pending in the United States Patent Office is the inventors' own work.

Moreover, the neuroprotective activity of G-CSF (in the context of a stroke model) is demonstrated already in DE 100 33 219 (paragraph [0009]: "The results show that G-CSF has neuroprotective properties. These were demonstrated both in the animal experiment, through a reduction of infarct area and of cerebral edema in the group treated with G-CSF, and in the cell culture, where glutamate damage was reduced by means of G-CSF.").

Accordingly, withdrawal of the rejection is requested.

Obviousness-type double patenting rejection

Applicants request that the provisional rejection under the doctrine of obviousness type double patenting in view of claims 1-5, 9-22 and 52-53 of co-pending application no. 10/880,101 be held in abeyance since the alleged conflicting claims have not yet been patented. Further, Applicants note the following from MPEP § 822.01:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

A Notice of Allowance is also requested.

Respectfully submitted,

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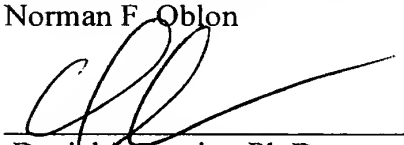

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